REMARKS

Claims 38 and 54-61 are pending and under examination in the pending Office Action. Claims 38 and 54-58 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tachado et al. (PNAS, USA, 94:4022-27, 1997) or Schofield et al. (Journal of Immunology, 156:1886-96, 1996). Claims 38 and 54-61 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement.

Alleged Anticipation Under 35 U.S.C. §102(b)

The Examiner has maintained the rejection of claims 38 and 54-58 in light of Tachado et al. (1997) or Schofield et al. (1996). It appears that the Examiner's rejection is principally based on the fact that the claims encompass GPI "derivative or equivalent" molecules that the Examiner alleges are disclosed in both cited references. However, Applicant respectfully disagrees with the rationale underlying this rejection under 35 U.S.C. §102(b).

Applicant respectfully submits that when mice are immunized with intact GPI molecules, such molecules generate antibodies to (a) the GPI lipid component (see Figure 1 of the present specification), (b) wherein said antibodies provide no protection against malarial disease (see Figure 2 of the present specification). In fact, such antibodies promote the onset and progression of disease processes by cross-reacting with, and thereby cross-linking, the host's GPI lipids (see Figures 4 and 5 of the specification). The result of this cross-linking is that cellular activation is induced (see Figure 5 of the specification), as are inflammatory cascades (see Figure 6 of the specification). Ultimately, this promotes disease in the host mice (see Figure 7 of the specification) rather than the dramatically opposite effect conferred by the antigenic glycan claimed herein, i.e., substantial protection against parasite infection. Therefore, in terms of the

present invention, Applicant has determined that where the GPI molecule is sufficiently delipidated prior to being administered to a mammal disease promoting anti-lipid antibodies are not generated. In stark contrast, anti-glycan antibodies protective against parasite infection are produced. In other words, the antibodies generated are directed to the carbohydrate domain of the GPI. These antibodies have been found to be protective (see Figure 8 of the specification).

Accordingly, and as discussed in Examples 16 and 17, anti-lipid antibodies do not distinguish between the lipid domains of a microorganism GPI versus the lipid domains of the endogenous mammalian GPI. This is in contrast to the behavior of antibodies directed to protein and carbohydrates antigens that are known to be capable of discriminating very fine structural distinctions between related protein or carbohydrate targets. Thus, it is the strongly hydrophobic targets, such as lipids, which result in the generation of antibodies that tend to be broadly cross-reactive and non-discriminatory. It is for this reason that antibodies which are directed to GPI lipids, despite the well-known structural differences which exist between these lipid structures readily cross-react.

The species of intact GPIs disclosed in Tachado et al. contain three lipids of similar chain length (at the sn1 position, the sn2 position and a lipid directly coupled to the inositol). See **Exhibit A.** The relevance of this to the present case is that Tachado's partially delipidated GPI structures were obtained by specific targeted enzymatic hydrolysis reactions. For example, hydrolysis with phospholipase A_2 (PLA_2) deacylates the lipid moiety specifically at the sn-2 position. See **Exhibit B.** Further, if the native GPI is hydrolyzed by phospholipase D, the entire glycerophospholipid moiety is removed, whereas the palmitic acid residue remains covalently bonded to inositol. **Exhibit C**. Thus, in Tachado et al., all of the products of GPI hydrolysis retained sufficient amounts of the lipid domain to induce an anti-lipid immune response, thereby

defining molecules which fall outside the scope of the presently claimed subject matter.

Stated another way, the non-discriminatory anti-lipid antibodies that are generated against any one of these lipid chains would cross-react with all of the microorganism lipid chains, in addition to those lipids of the host GPI molecules. In this regard, it is important to understand that the hydrolyzed GPI structures described in Tachado et al. were problematic. That is, there was at least one lipid which remained intact and against which anti-lipid antibodies could be generated and would therefore function adversely by virtue of their cross-reactivity to all GPI lipid molecules. Therefore, by specifying that the GPI molecules of the present invention contain "insufficient lipid domain to elicit or induce an immune response" we believe that the structures that are disclosed by Tachado et al. are clearly not within the scope of the claims.

In conclusion, it is respectfully submitted that the foregoing remarks explain with particularity, why the partially hydrolyzed lipids of Tachado et al. are not encompassed by the compositions claimed herein. Put another way, in view of the immunostimulatory differences between Tachado's compounds and those encompassed by the subject disclosure, it is clear that Tachado's partially delipidated species of GPIs are inherently incapable of eliciting the protective immunological responses. Therefore, the subject specification provides a bio-assay based on *in vivo* criteria (i.e., production of antibodies) for distinguishing the structural features of Tachado's GPIs and those species that are effective in the claimed compositions.

With respect to Schofield et al., the Examiner alleges that the reference discloses "a GPI of malaria parasite origin" and a "mAb to malarial GPI (p. 1887)."

It is respectfully submitted that that this reference does not disclose preparation of the immunogenic portion of the GPI that provides protective immunity. Further, the antibody referenced in Schofield et al., does not possess the properties encompassed by antibodies

obtained by immunization with the claimed composition.

Accordingly, the GPI glycan moiety, and the protective antibodies obtained by immunizing mice with it, are not disclosed in either Tachado et al., or Schofield et al. Neither reference discloses each limitation of the pending claims, and therefore, cannot anticipate the claimed subject matter.

Accordingly, withdrawal of the rejection based on Tachado et al. and Schofield et al., respectfully requested.

Alleged Lack of Written Description Under 35 U.S.C. §112, First Paragraph

Claims 38 and 54-61 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement.

The Examiner alleges that the specification does not provide sufficient description of all of the possible different species of GPI molecules, equivalents and derivatives, encompassed by the claims.

Applicant respectfully disagrees with the Examiner's unduly rigid application of the written description requirement. However, in order to expedite the allowance of the subject application, claim 38 has been amended to further define the derivative or equivalent encompassed by the claimed subject matter possess at least three residues of the core glycan portion of the modified GPI domain.

Support for this claim amendment can be found in the various glycan embodiments of the illustrated on pages 28-46 of the specification, as well as in claim 61.

The scope of the claims as amended is now further defined by specifying a structural feature of the modified GPIs, derivatives and equivalents, i.e., they possess at least three of the

glycan's core residues. It is respectfully submitted that persons of ordinary skill in the art would appreciate that the claimed invention, as recited in the amended claims, was within the possession of the inventor at the time of filing this application.

The Examiner also specifically alleges that claim 60, directed to a modified GPI having any tetrapeptide linked to the ethanolamine moiety is inadequately supported by the specification. For example, the Examiner believes that the number of species of tetrapeptides (approximately 160,000) encompassed by the claim is not supported.

Applicant respectfully submits that a 4-mer peptide linked to GPI is an additional element that is not believed to affect the antigenicity of a modified GPI molecule or perturb the primary function of the claimed composition, i.e., to elicit an anti-parasite protective immune response; and the modified GPI molecule is the core feature of the present invention which is adequately described.

Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited. Should the Examiner believe that a telephone discussion would help clarify any issues or expedite the allowance of the application, the Examiner should feel free to contact the undersigned at any time.

Respectfully submitted,

Xiaochun Zhu
Registration No.: 56,311

Scully, Scott, Murphy & Presser, P.C.
400 Garden City Plaza- Suite 300
Garden City, New York 11530
(516) 742-4343
XZ/TG:eh/ab

EXHIBIT A

Figure 1

P. falciparum GPI structure (complete)

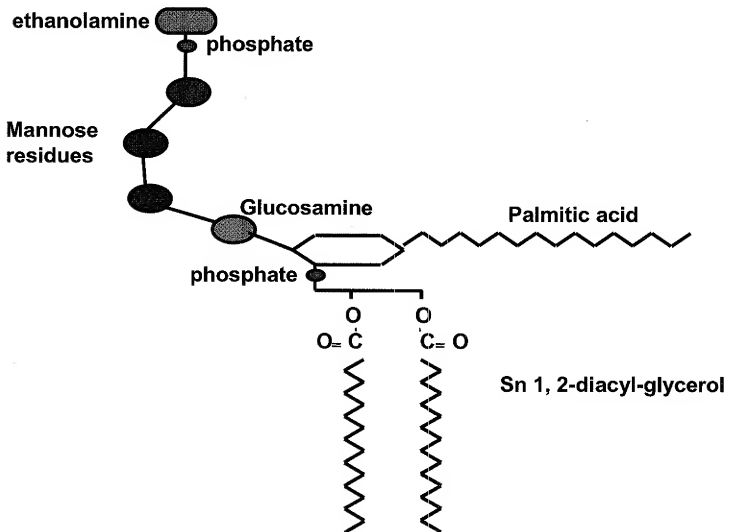

EXHIBIT B

Figure 2

Partial GPI structure following PLA_2 hydrolysis

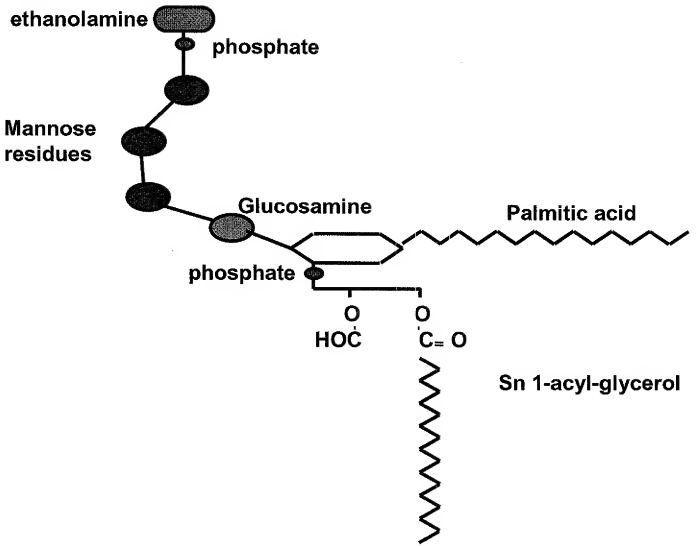

EXHIBIT C

Figure 3

Partial GPI structure following GPI-PLD hydrolysis